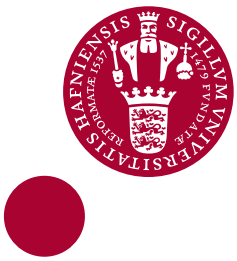

International consensus statement on the peri-operative management of anaemia and iron deficiency

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Consensus Statement

International consensus statement on the peri-operative management of anaemia and iron deficiency

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Summary

Despite current recommendations on the management of pre-operative anaemia, there is no pragmatic guidance for the diagnosis and management of anaemia and iron deficiency in surgical patients. A number of experienced researchers and clinicians took part in an expert workshop and developed the following consensus statement. After presentation of our own research data and local policies and procedures, appropriate relevant literature was reviewed and discussed. We developed a series of best-practice and evidence-based statements to advise on patient care with respect to anaemia and iron deficiency in the peri-operative period. These statements include: a diagnostic approach for anaemia and iron deficiency in surgical patients; identification of patients appropriate for treatment; and advice on practical management and follow-up. We urge anaesthetists and peri-operative physicians to embrace these recommendations, and hospital administrators to enable implementation of these concepts by allocating adequate resources.

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Recommendations for best clinical practice

1 Physicians should consider pre-operative anaemia and iron deficiency as an indication for a peri-operative care pathway that stretches from the decision to operate until complete recovery from surgery.
2 The presence of anaemia should be investigated in all surgical procedures with expected moderate-to-high blood loss (> 500 ml).
3 Serum ferritin level < 30 $\mu g.l^{-1}$ is the most sensitive and specific test used for the identification of absolute iron deficiency. However, in the presence of inflammation (C-reactive protein > 5 $mg.l^{-1}$) and/or transferrin saturation < 20%, a serum ferritin level < 100 $\mu g.l^{-1}$ is indicative of iron deficiency.
4 Major, non-urgent surgery should be postponed to allow the diagnosis and treatment of anaemia and iron deficiency.
5 When treating anaemia pre-operatively, the target haemoglobin concentration should be ≥ 130 $g.l^{-1}$ in both sexes, to minimise the risk of transfusion-associated unfavourable outcomes
6 Oral iron replacement should be targeted to patients with iron deficiency with or without anaemia whose surgery is scheduled 6–8 weeks after diagnosis, preferably by the primary care physician (General Practitioner).
7 Daily (40–60 mg) or alternate-day (80–100 mg) treatment with oral iron and nutritional advice should be initiated immediately in patients with iron deficiency and no contra-indications.
8 Sufficient data exist to support intravenous iron as efficacious and safe. Intravenous iron should be used as front-line therapy in patients who do not respond to oral iron or are not able to tolerate it, or if surgery is planned for < 6 weeks after the diagnosis of iron deficiency.
9 The diagnosis and treatment of anaemia and iron deficiency should commence as early as possible in the peri-operative period, and ideally as soon as the decision to undertake surgery is made.

Why was this consensus statement developed?

Several guidelines for the management of peri-operative anaemia have been published over the last decade [1–11]. However, for anaemia and iron deficiency in adult surgical patients, there are a number of non-evidence based misconceptions regarding prevalence, consequences, diagnosis and treatment, as well as inconsistency of terminology and lack of clear guidance on clinical pathways. Throughout surgical practice, there has been increased emphasis on speed to operation, and many pre-assessment clinics focus on the ability to facilitate same-day hospital admissions, which may overlook potential opportunities to optimise patients, and improve fitness for surgery.

How does this consensus statement differ from other available guidelines?

There are a number of guidelines from professional associations recommending 'what to do' [1–11]. The aim of this document is to utilise the recommendations therein, and provide a working practice document on 'how to' feasibly introduce these guidelines into clinical practice; or better stated, how to do it. Therefore, our goal is to provide independent, collective guidance and a pragmatic, clear clinical pathway for the diagnosis and treatment of peri-operative iron deficiency and anaemia in adult surgical patients, in order to improve outcomes in a cost-effective manner.

Iron deficiency

Iron is the most common and widespread nutritional deficiency, even in industrialised countries, and affects

approximately two billion people worldwide [12, 13]. Iron deficiency, with or without anaemia, is associated with chronic conditions such as cancer (43% across different tumours), inflammatory bowel disease (45%), chronic kidney disease (24–85%), chronic heart failure (43–100%) and other chronic inflammatory diseases [14].

Apart from its well-recognised role in erythropoiesis, iron is also a critical component in many important cellular processes such as oxygen transport, electron transfer reactions, mitochondrial respiration, gene regulation and cellular immunity [15, 16]. Functional iron deficiency in critically ill patients is associated with an increased duration of systemic inflammatory response syndrome and prolonged ICU stay [17]. In congestive heart failure, iron deficiency has been independently associated with compromised physical performance and quality of life [18], as well as an increase in all-cause and cardiovascular mortality [19]. Treatment of iron deficiency with i.v. iron may improve functional status within 4 weeks, which has been shown to be maintained after 24 and 52 weeks [20, 21].

Importantly, in a large series of non-cardiac surgical patients (n = 2115; 48% women), the prevalence of anaemia was 34%, and absolute iron deficiency and iron sequestration (see below) was responsible for 75% of the cases of anaemia (541/715) [22]. In addition, before major orthopaedic or abdominal surgery, low ferritin levels have been associated with increased rates of postoperative infections [23, 24].

For a 70-kg man, total body iron is about 3500 mg (50 $mg.kg^{-1}$ body weight). Most of the iron in the body is distributed in haemoglobin (Hb) within red blood cell (65%; 2300 mg). Approximately 10% is found in muscle fibres (in myoglobin) and other tissues (in enzymes and cytochromes) (350 mg). The remaining iron is stored in the liver, macrophages and bone marrow (850 mg) [25]. The amount of iron required for the daily production of 300 billion red blood cells (20–30 mg) is provided mainly by macrophages recycling iron from senescent red blood cells (RBC), while daily iron absorption (1–2 mg) balances daily losses. Increased iron requirements, limited external supply and increased blood loss may lead to progressive iron deficiency and, subsequently, iron deficiency anaemia [25] (Table 1). Thus, different types (stages) of iron deficiency are found in surgical patients (Table 2), classified as follows:

- Inadequate (low) iron stores; this refers to the body's inability to sustain erythropoiesis to recover from blood loss at operation. This may be indicated by the serum ferritin level; in a healthy adult, 1 $ng.l^{-1}$ ferritin reflects approximately 8 mg stored iron [26]. As an example, a patient with a pre-operative ferritin < 100 $ng.l^{-1}$ may not have enough iron reserves to recover from a 30–40 $g.l^{-1}$ Hb drop, while maintaining normal iron stores (ferritin > 30 $ng.l^{-1}$).
- True (absolute) iron deficiency without anaemia refers to a reduction in total body iron with normal Hb, as levels of erythroid iron are still sufficient for erythropoiesis. This condition is often seen in women of child-bearing age.
- Iron deficiency anaemia refers to a more severe condition in which decreased iron stores result in decreased Hb and usually microcytic hypochromic red cells (mean corpuscular volume < 80 fl; mean corpuscular haemoglobin < 27 pg). The corrected

Table 1 Main causes of iron deficiency.

A. Increased demand
• Growth during infancy and childhood
• Treatment with erythropoiesis-stimulating agents
B. Limited supply
• Poor intake
• Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid
• Malabsorption
– Gastric resection
– *Helicobacter pylori* infection (even without significant bleeding)
– Malabsorption syndromes (Crohn's disease and celiac disease)
• Drug interference (gastric anti-acid agents and antisecretory drugs)
C. Increased losses
• Phlebotomy
– Blood donation
– Dialysis (particularly haemodialysis)
• Haemorrhage
– Surgery
– Trauma
– Gastrointestinal bleeding
– Genitourinary bleeding
– Respiratory tract bleeding

Table 2 Characteristics of the different stages of iron deficiency in surgical patients.

Iron status	Laboratory findings	Initial treatment	Adjuvant treatment
Normal	Ferritin 30–300 $\mu g.l^{-1}$ TSAT 20–50% CRP < 5 $mg.l^{-1}$	None	None
Low iron stores (for surgery with moderate-to-high blood losses)	Ferritin < 100 $\mu g.l^{-1}$	Low dose oral iron (40–60 mg iron per day or 80–100 mg alternate days, 6–8 weeks)	Intravenous iron, if intolerance, contraindication or no response to oral iron or short time to surgery
Iron deficiency	Ferritin < 30 $\mu g.l^{-1}$	Low dose oral iron (40–60 mg iron per day or 80–100 mg alternate days, 6–8 weeks)	Gastro-intestinal/urological investigations Intravenous iron, if intolerance, contraindication or no response to oral iron or short time to surgery
	*Ferritin 30–100 $\mu g.l^{-1}$ TSAT < 20% and/or CRP > 5 $mg{\cdot}l^{-1}$	Intravenous iron (Calculated dose)†	Treat underlying chronic disease if possible Recombinant erythropoietin in the selected case if anaemia does not respond to i.v. iron alone
Functional iron deficiency*	Ferritin 100–500 $\mu g.l^{-1}$ TSAT < 20%	Intravenous iron (Calculated dose)†	Revise erythropoietin dose Check folic acid and vitamin B_{12}
Iron sequestration*	Ferritin > 100 $\mu g.l^{-1}$ TSAT < 20% and/or CRP > 5 $mg.l^{-1}$	Recombinant erythropoietin, if anaemia	Intravenous iron, if functional iron deficiency develops

CRP, C-reactive protein; Fe, elemental iron; TSAT, transferrin saturation index.
*Low reticulocyte Hb content (CHr < 28 pg), high proportion of hypochromic red cells (HYPO > 5%), low RBC size factor (RBCSF < 88 fl) or ferritin index > 2 will confirm a component of iron deficiency.
†Total iron deficiency [mg] = (Target Hb − Baseline Hb [$g.l^{-1}$]) · 0.24 · Body weight [kg] + 500. A simplified calculation is 200 mg per each 10 $g.l^{-1}$ of Hb deficit respect to target Hb + 500 mg for stores.

reticulocyte count provides an estimate of the rate of effective marrow production compared with normal (set as a production index of 1). A production index greater than 2 is not compatible with iron deficiency anaemia.

- Functional iron deficiency: this refers to insufficient mobilisation of iron from stores due to increased demands, in the presence of normal or elevated iron stores. It is clearly defined in renal patients following treatment with erythropoiesis-stimulating agents [15].
- Iron sequestration: this refers to decreased iron mobilisation from the stores in the liver and the macrophages to meet daily bone marrow requirements. This is caused by inflammation, which up-regulates hepatic hepcidin synthesis and may decrease the synthesis and activity of erythropoetin. Hepcidin binds to ferroportin, the only known iron-exporting protein in humans, and promotes its internalisation and degradation, resulting in inhibition of intestinal iron absorption and iron sequestration at liver and macrophages [25] (Fig. 1). This may evolve to true iron deficiency in patients with inflammation and chronic blood losses.

Diagnosis of iron deficiency

Serum ferritin and transferrin saturation (TSAT) are commonly used for an initial evaluation of iron status. Serum ferritin level is the most widely-used test for evaluating iron stores, while TSAT reflects iron availability for erythropoiesis (TSAT < 20% indicates insufficient iron supply to support normal erythropoiesis). C-reactive protein (CRP) is a marker of inflammation which is useful when iron-restricted erythropoiesis due to iron sequestration is suspected [25, 26]. Thus:

- A serum ferritin level < 30 $\mu g.l^{-1}$ is the most sensitive (92%) and specific (98%) cut-off level for the identification of true iron deficiency (with or without anaemia); no further laboratory work-up is needed (Fig. 2) [15, 25, 27].

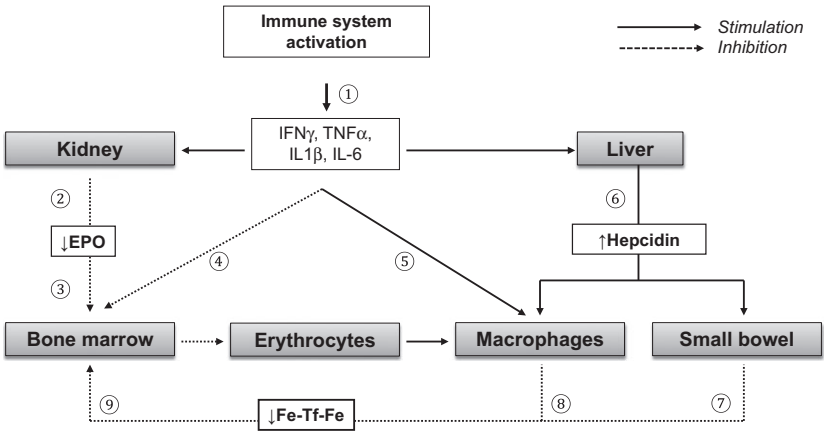

Figure 1 Effects of inflammation on iron metabolism and erythropoiesis. 1, release of immune and inflammatory cytokines; 2, decreased erythropoietin (EPO) production; 3, decreased erythropoietic stimulation; 4, inhibition of erythroid cell proliferation; 5, augmented erythrophagocytosis; 6, IL-6 induced hepcidin release; 7 & 8, decreased ferroportin-mediated release of iron from enterocytes (inhibition of iron absorption) and macrophages (iron sequestration), leading to decreased transferrin-bound iron; 9, decreased iron availability for erythropoiesis.

- In the presence of inflammation (CRP > 5 mg.l^{-1}), and/or TSAT < 20%, ferritin < 100 μg.l^{-1} strongly suggests iron deficiency (see below) (Fig. 2). It also indicates inadequate iron stores for surgery during which moderate-to-high blood loss is expected.
- In contrast, TSAT < 20% and ferritin > 100 μg.l^{-1} usually indicates iron sequestration, as seen in inflammatory conditions (CRP > 5 mg.l^{-1}), or functional iron deficiency, as seen during treatment with erythropoiesis-stimulating agents (Table 1; Fig. 2) [25].

However, although ferritin values > 100 μg.l^{-1} argue against concurrent true iron deficiency in the setting of inflammation, due to its acute phase reactivity, its diagnostic value is imperfect. Other tests, such as low reticulocyte Hb content (CHr < 28 pg) or an increase in hypochromic red cells (Hypo > 5%), can be utilised to evaluate for a component of iron deficiency, which if present suggests iron supplementation may be beneficial [25, 28]. The ratio of serum transferrin receptor level to the log of ferritin (sTfr/log Ft), the so-called ferritin index, may be used when these automated red cell parameters are not routinely available [25, 28]. A ferritin index > 2 indicates true iron deficiency, and is a strong predictor of response to i.v. iron [28, 29]. Detailed information regarding the advantages, disadvantages, limitations and diagnostic values of these parameters can be found elsewhere [30].

Anaemia

Anaemia is defined by the World Health Organization as an Hb concentration < 130 g.l^{-1} for men, < 120 g.l^{-1} for non-pregnant women and < 110 g.l^{-1} for pregnant women [31]. These definitions are widely quoted and accepted, and are used in most epidemiological studies. They are also adopted in most blood conservation guidelines, where no further laboratory work-up is deemed necessary for non-anaemic patients.

However, we consider that this may not be reliable for the classification of non-pregnant women undergoing surgical procedures in which moderate-to-high blood loss is expected. Women have lower circulating blood volumes than men, but the same procedures performed in either sex often result in comparable amounts of blood loss. Therefore, when measured as a proportion of circulating blood volume, blood losses are proportionally higher in women and may result in higher transfusion rates, as corroborated by a study in orthopaedic surgery [32] and the first Austrian benchmark study [33]. As women with a pre-operative Hb of 120 g.l^{-1} are twice as likely to require a transfusion as men with an Hb of 130 g.l^{-1}, this Hb level should be considered as suboptimal in surgical settings. In

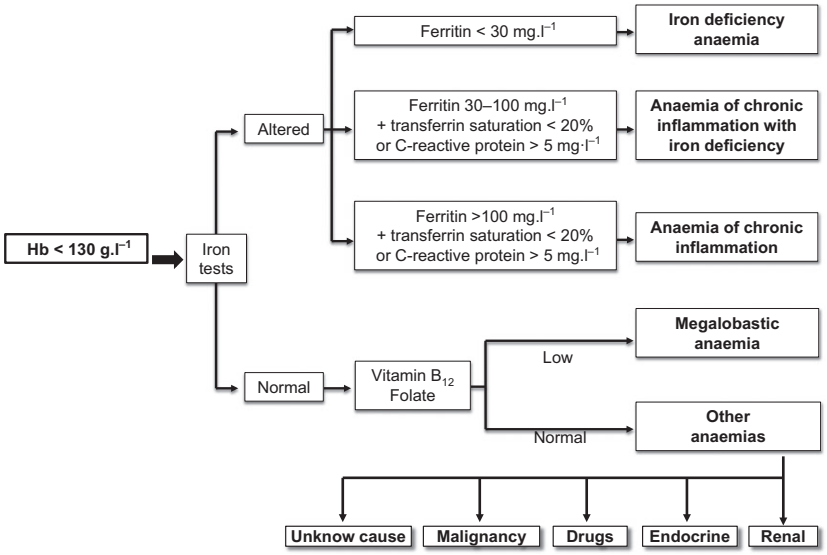

Figure 2 Algorithm for classification of peri-operative anaemia.

cardiac surgery, a 10 g.l^{-1} decrease in Hb has been shown to be independently associated with increased transfusion requirements, increased mortality and prolonged hospital stay [34].

Consequently, apart from replenishing iron stores, pre-operative treatment of iron deficiency anaemia should be aimed at producing a target Hb level ≥ 130 g.l^{-1} in both sexes, to minimise the risk of transfusion-associated unfavourable outcomes [35].

Patients who are anaemic and require major surgery (including the obstetrics and gynaecology population), especially if moderate to high blood loss (> 500 ml) is likely and/or if there is a ≥ 10% statistical probability for red blood cell (RBC) transfusion, should be investigated (Fig 3). Laboratory investigations should be performed as early as possible in the pre-operative period in order to implement the most appropriate treatment, if needed. They should initially include at least full blood count, serum ferritin, TSAT, a marker of inflammation (e.g. serum CRP) and a marker of renal function (e.g. serum creatinine), which can be easily requested by a surgeon (at the time of listing for surgery), an anaesthetist (during the pre-anaesthesia assessment) or a primary care physician/general practitioner. In some hospitals, there is also the possibility of automatically ordering additional laboratory tests when an Hb < 130 g.l^{-1} is detected by pre-operative analysis.

Intervening to treat pre-operative iron deficiency anaemia in the surgical patient can be expected to reduce the number of transfusions given and thereby improve outcomes, even in those for whose anaemia, surgery is the cure. There is good evidence that attempts to correct iron deficiency anaemia pre-operatively will improve Hb before surgery, but there is little good quality evidence that it can modify the excess of risk for postoperative complications, other than those associated with transfusion [28, 36–42]. However, moderate to severe anaemia (Hb < 110 g.l^{-1}) results in worse outcomes than milder anaemia [43]. In contrast, there is also good evidence that correcting anaemia by transfusing blood can be detrimental to the outcomes of surgery [37, 44, 45].

Despite the lack of level-one evidence for improved outcomes, it is still recommended as good clinical practice to treat all surgical patients with pre-operative iron deficiency anaemia, but with a particular emphasis on treating those undergoing major surgery. Patients undergoing more minor surgical procedures are unlikely to see wide fluctuations in Hb postoperatively, and surgery can proceed while anaemia evaluation and treatment is ongoing.

Patients who have absolute iron deficiency should also be investigated for gastro-intestinal pathology (Table 1). The prevalence of other haematinic deficiencies before elective major orthopaedic surgery is

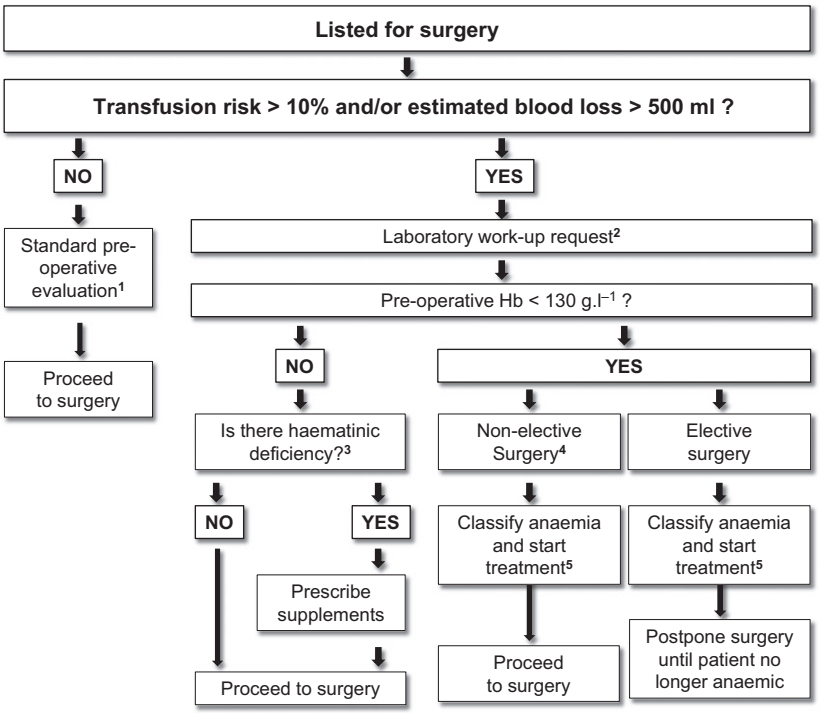

Figure 3 Algorithm for the management of a surgical patients. 1, According to centre protocol for each surgical procedure; 2, It should initially include at least full blood counts, serum ferritin, transferrin saturation, a marker of inflammation (e.g. serum C-reactive protein) and a marker of renal function (e.g. serum creatinine); 3, Haematinic deficiencies are defined by ferritin < 100 $\mu g \cdot l^{-1}$, vitamin B_{12} < 270 $pg \cdot ml^{-1}$ and/or folate < 3 $pg \cdot ml^{-1}$; 4, Including patients presenting late before surgery and non-deferrable surgery (e.g. cancer surgery); 5, According to algorithm depicted in Fig. 2.

approximately 12% for vitamin B_{12} [defined by serum concentration < 270 $pg.ml^{-1}$ (200 $pmol.l^{-1}$)], and 3% for folate [defined by serum concentration < 3 $ng.ml^{-1}$ (5 $nmol.l^{-1}$)] [46]. If none are found, other causes of anaemia should be ruled out (Fig. 2).

Treatment

Treatment of pre-operative iron deficiency anaemia should be implemented as early as possible before the scheduled surgical procedure. Most major surgery is elective. In the UK, the recent NHS Blood and Transplant audit showed there was a median of 60 days from listing the patient for surgery to the operation itself (http://hospital.blood.co.uk/audits/national-comparative-audit/). Thus, treatment of iron deficiency anaemia should be attempted while the patient is on the surgical waiting list, although this is currently rarely practised [47].

Regarding oral iron, in non-anaemic iron-deficient women, high doses of iron sulphate stimulate hepcidin release, which results in lower iron absorption from the next daily dose [48]. In contrast, it appears that low-dose (≤ 60 mg) oral iron given on alternate days may maximise fractional iron absorption, increase dosage efficacy, reduce gastro-intestinal exposure to unabsorbed iron and ultimately improve tolerance and adherence to treatment [48]. As anaemia-induced hypoxia and erythropoietin production downregulate the expression of hepcidin [15, 25], this may counterbalance the stimulatory effect of iron. In octogenarian patients with iron deficiency anaemia, 50 mg or 150 mg iron sulphate daily for 2 months both improved Hb and ferritin levels equally, but fewer side-effects were observed with the lower dose [49]. Therefore, when the interval before surgery is sufficient (at least 6–8 weeks) and no contra-indications are present, daily (40–60 mg) or alternate-day (80–100 mg) supplementation with oral iron and nutritional advice may be appropriate. The actual dose may depend upon the elemental iron content of the available oral iron

formulation, which differs depending on country of manufacture.

However, many patients will not respond to oral iron, especially those with functional iron deficiency and chronic illness or infection and those with ongoing blood loss [15, 25]. Others will not tolerate oral iron due to gastro-intestinal side-effects. Once oral iron has been commenced, the Hb should be measured again, at least 4 weeks before surgery. In the absence of an increased Hb or if the patient is intolerant, i.v. iron is the preferred replacement route. If surgery is planned in less than 6 weeks time, i.v. iron may also be the most effective option.

Intravenous iron is highly efficacious at replenishing iron stores and increasing Hb in anaemia due to iron deficiency with or without inflammation (Fig. 2). The dose of i.v. iron may be calculated from the baseline and target Hb and patient's body weight, adding 500 mg for iron stores (in patients > 35 kg) [25]. In practice, a dose of 1000–1500 mg is sufficient in most surgical patients and can usually be given by slow infusion over less than 1 h in one sitting or in two divided doses, depending on the preparation used. Most patients feel better in 3 days, with a rapid Hb response (50% at 5 days, 75% at 10–14 days, maximal at 3 weeks) [50].

In a small series, i.v. iron sucrose before orthopaedic surgery has been shown to be useful for treating iron deficiency anaemia, with a maximum effect on Hb after 2 weeks [51]. In abdominal surgery, i.v. iron carboxymaltose (1000 mg) 2–4 weeks [40, 42] or 8–10 days pre-operatively [41] has been shown to decrease RBC transfusion and hospital stay.

Intravenous iron treatment < 2 weeks pre-operatively has also been shown to be successful in decreasing the need for RBC transfusion, acute kidney injury, hospital stay and infections in orthopaedic and cardiac surgery [52, 53]. A quicker recovery in Hb postoperatively was also observed in iron-deficient patients treated with i.v. iron sucrose [54] or carboxymaltose [41, 42]. Administration of i.v. iron isomaltoside (1000 mg) 1 day before or even on the day of surgery can improve postoperative Hb recovery even in non-anaemic patients without iron deficiency [55].

Presently, there is a lack of high-quality data about effect on outcomes, but a number of large randomised, controlled trials are in progress [56].

Iron deficiency without anaemia

A recent meta-analysis of 21 trials in different clinical settings concluded that there is emerging evidence that non-anaemic iron deficiency is a disease in its own right, deserving of further research in the development of strategies for detection and treatment [57]. Non-anaemic patients with iron deficiency or inadequate iron stores undergoing surgical procedures with expected moderate-to-high blood loss may benefit from pre-operative iron administration, to boost recovery from postoperative anaemia [1, 3] (Fig. 2). In those with absolute iron deficiency (ferritin < 30 $\mu g.l^{-1}$), the need for gastro-intestinal investigations should be considered [3]. Microcytosis due to iron deficiency without anaemia should be evaluated for chronic hypoxaemia, myeloproliferative disease (e.g. polycythaemia rubra vera), or another cause of increased red cell production. Iron replacement may cause a surge in Hb that could induce hyperviscosity in this subgroup.

In non-anaemic orthopaedic surgical patients, the administration of iron ferrous sulphate and vitamins during the weeks preceding surgery has been shown to increase serum ferritin and transferrin saturation [58] and reduce transfusion [59]. However, adherence to iron supplementation was 67%, and adverse drug reactions were present in 52% of patients [60].

In women undergoing major non-cardiac surgical procedures, the prevalence of true iron deficiency (ferritin < 30 $\mu g.l^{-1}$) for Hb 120–129 $g.l^{-1}$ was similar to that for Hb < 120 $g.l^{-1}$, and significantly higher than for Hb ≥ 130 $g.l^{-1}$ (42%, 51% and 24%, respectively; $p < 0.05$). This also applies to insufficient iron supply for erythropoiesis, as defined by TSAT < 20% (58%, 69% and 34%, respectively; $p < 0.05$) [22]. Thus, although considered as non-anaemic according to WHO definitions [31], most women with Hb 120–129 $g{\cdot}l^{-1}$ would benefit from iron replacement therapy, for optimising pre-operative Hb levels and facilitating recovery from postoperative anaemia.

For non-anaemic patients undergoing surgery with a high risk for developing severe postoperative anaemia, we suggest the administration of oral iron. Intravenous iron administration (e.g. 500 mg) should be considered if surgery is scheduled to take place in < 4 weeks or if the patient cannot tolerate oral iron [1].

Delaying surgery

As stated above, uncorrected pre-operative anaemia is a risk factor for poor outcome [61–66]. Although there is little evidence currently that treatment of iron deficiency anaemia improves outcome [60, 67], it does reduce transfusion and may reduce hospital stay. Consequently, there is considerable uncertainty as to whether surgery should be delayed in patients with undiagnosed/untreated anaemia.

The problem may be divided into patients undergoing surgery for benign vs. malignant disease. In major surgery for benign disease, especially when blood loss > 500 ml is expected or possible, patients should be informed about the relationship between anaemia, morbidity and mortality, and should be given the opportunity to postpone non-urgent surgery until their anaemia is investigated and treated [4, 35]. Several guidelines recommend postponing the operation for about 4 weeks to allow appropriate management of anaemia [1, 2, 4, 8].

In some European countries, the allowable time between diagnosis and surgery for malignant disease is subjected to legal regulations. Nevertheless, many receive pre-operative adjuvant therapy, which allows sufficient time for concurrent treatment of pre-operative iron deficiency anaemia.

Postoperative anaemia

Anaemia is present in up to 90% of patients in the immediate postoperative period after major surgery [68]. The main causes are: presence of pre-operative anaemia; peri-operative blood loss; poor nutritional intake in the postoperative period; and frequent blood sampling for laboratory tests. In addition, increased hepcidin due to the inflammatory response to surgery can lead to inhibition of iron absorption from the small bowel and reduced iron release from stores (iron sequestration) [25] (Fig. 1). These effects can last for a few weeks after major surgery and aggravate postoperative iron deficiency anaemia.

Recently, the National Institute for Clinical Excellence [69] and other international guidelines [4, 5, 70] have reduced the transfusion thresholds for surgical patients to 70 $g.l^{-1}$ (80 $g.l^{-1}$ for patients with a history of ischaemic heart disease) in the absence of active bleeding. This change in practice has led to more patients being discharged with significant anaemia after major surgery. Therefore, it is important to implement strategies for postoperative anaemia management.

Management of iron deficiency with oral iron in the immediate postoperative period has a very limited role due to poor absorption and considerable side-effects, and is not recommended [4]. In contrast, i.v. iron has been successfully used to treat iron deficiency anaemia after surgery for lower limb arthroplasty [71], gastrectomy [72] and postpartum haemorrhage [73]. The administration of a single 1000-mg dose of ferric carboxymaltose after major orthopaedic surgery, abdominal and genito-urinary surgery, and others, has been shown to correct anaemia and improve quality of life compared with oral iron [74, 75].

Transfused packet RBC contains haem iron (200–250 mg per unit), plus a small amount of labile iron which is immediately available for erythropoiesis; in part, dependent on the storage time of the transfused RBC unit [76]. After transfusion, the patient's Hb is usually < 10 $g.l^{-1}$. Correcting postoperative iron deficiency, in addition to RBC transfusion to raise Hb, may be important to improve function, as shown in animal models [77]. Further research is required as to whether supplemental iron given to correct iron deficiency in patients who are transfused peri-operatively is beneficial in humans.

Safety of i.v. iron therapy

Currently, six i.v. iron formulations are available in the USA and/or Europe (Table 3), and serious adverse events (SAEs) are very rare (38 per 10^6 administrations; deaths, 0.4 per 10^6 administrations) [78]. In contrast, the most recent Serious Hazards of Transfusion Report in the UK quotes the risk of death related to transfusion as 1 in 100,000, and the risk of major morbidity as 1 in 16,000 [79]. The European Medicines Agency concluded that the benefits of i.v. iron exceed the risks when used appropriately (correct indication and dose), without any difference in safety profile among available formulations [80]. In line with these recommendations, guidance for risk minimisation and management of hypersensitivity reactions to i.v. iron has been recently published [81].

Table 3 Characteristics of different i.v. iron formulations.

	Iron gluconate**	Iron sucrose††	Low molecular weight iron dextran (LMWID)‡‡	Ferric carboxymaltose§§	Iron isomaltoside 1000¶¶	Ferumoxytol***
Brand name	Ferrlecit®	Venofer®	Cosmofer® INFeD®	Ferinject® Injectafer®	Monofer® Monoferro®	FeraHeme® Rienso®
Carbohydrate shell	Gluconate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide	Isomaltoside (linear oligosaccharide)	Polyglucose sorbitol carboxy-methylether
Complex type*	Type II	Type II	Type I	Type I	Type I	Type I
Molecular weight; kD	289–440	30–60	165	150	150	750
Initial distribution volume; l	6	3.4	3.5	3.5	3.4	3.16
Plasma half-life; h	1	6	20	16	20	15
Labile iron (% injected dose)†	3.3	3.5	2.0	0.6	1.0	0.8
Iron content; mg.ml^{-1}	12.5	20	50	50	100	30
Maximal single dose; mg	125	200	20 mg.kg^{-1}	20 mg.kg^{-1} (max 1000 mg)	20 mg.kg^{-1}	510
Infusion time for 1000 mg; min‡	720	300	90–150§	≥ 15	≥ 15	≥ 15
Product cost per 1000 mg; €¶	–	128	100	227	212	162

*Type I, robust and strong; Type II, semirobust and moderately strong; Type III, labile and weak (Crichton RR, Danielson BG, Geisser P. Iron therapy with special emphasis on i.v. administration, 4th Ed. UNI-MED Verlag AG, Bremen, 2008).
†Jahn MR, et al. Eur J Pharm Biopharm 2011; 78:480–91.
‡Includes 30-min postinfusion observation.
§Safe administration of 1000 mg LMWID in 1 h has been described (Auerbach M et al. Am J Hematol 2011; 86:860–2).
¶British National Formulary BNF68, September 2014 – March 2015. BMJ Group and the Royal Pharmaceutical Society of Great Britain, London, 2014.
**Ferrlecit summary of product characteristics. http://www.products.sanofi-aventis.us/ferrlecit/ferrlecit.pdf (accessed 01/08/2016).
††Venofer summary of product characteristics. http://www.luitpold.com/documents/22.pdf (accessed 01/08/2016).
‡‡Comofer summary of product characteristics. http://www.cosmofer.com/product/cosmofer-spc/cosmofer-spc.aspx (accessed 01/08/2016).
§§Ferinject summary of product characteristics. http://www.ferinject.co.uk/smpc/ (accessed 01/08/2016).
¶¶Monofer summary of product characteristics. http://www.monofer.com/spc.aspx (accessed 01/08/2016).
***FeraHeme summary of product characteristics. http://www.feraheme.com/pdfs/Feraheme_Prescribing_Information.pdf (accessed 01/08/2016).

Some patients who receive i.v. iron may exhibit complement activation-related pseudo-allergy, which should not be misinterpreted as hypersensitivity. This occurs in approximately 1:200 iron-treated patients, and can consist of arthralgia, myalgia or flushing, but without associated hypotension, tachycardia, tachypnoea, wheezing, stridor or peri-orbital oedema [82]. Symptoms abate without intervention, and the patient may be rechallenged or another i.v. iron formulation tried [82].

A recent meta-analysis of 103 trials published from 1965 to 2013 (including 19,253 patients) concluded that i.v. iron therapy was not associated with an increased risk of serious adverse events or infection when compared with oral or intramuscular iron, no iron or placebo [83]. In large observational studies, peri-operative i.v. iron did not negatively impact on rates of transfusion, infection and 30-day mortality in surgical patients [51, 84]. In contrast, red cell transfusion delivers haem and labile iron which supports bacterial growth more readily [85].

The preponderance of published evidence indicates that i.v. iron is safe, supporting a greater and earlier role for treating iron deficiency and raising the question of whether parenteral iron should be considered for front-line therapy in conditions where oral iron will predictably fail. However, further prospective efficacy and safety trials in various surgical settings are required to make evidenced-based conclusions [82].

Cost implications of iron therapy

There are few studies that have undertaken formal cost–benefit analysis of iron treatment. Bhandari et al. [86] performed a comparative analysis of the costs of administering i.v. iron formulations against RBC transfusion, by considering acquisition costs plus administration costs (nursing time and giving sets) and transportation to hospital, across three dosage levels (600 mg, 1000 mg and 1600 mg). At all doses, i.v. iron resulted in a net saving when compared with RBC transfusion, with the biggest differences observed for ferric carboxymaltose and iron isomaltoside-1000.

Calvet et al. [87] compared the cost implications of ferric carboxymaltose vs. iron sucrose vs. oral iron for avoiding red cell transfusion in 282 patients with colorectal cancer and anaemia, using cost-minimisation analysis. Direct and indirect costs for acquisition and administration of iron product and RBC concentrates, as well as hospitalisation costs, were included in the cost model. Ferric carboxymaltose reduced hospital stay by 2.3 days compared with iron sucrose and by 2.6 days compared with oral iron, resulting in cost savings of £437 (485€, $532) and £245 (274€, $300) per patient, respectively.

Data from 182 matched pairs of total lower limb arthroplasty patients, managed with a restrictive transfusion protocol and without (control) or with postoperative i.v. iron, were retrospectively reviewed [88]. Acquisition and administration costs of iron (600 mg iron sucrose or ferric carboxymaltose) and RBC concentrates, Hb, and prolonged stay in hospital were used. Patients receiving RBC transfusion stayed in hospital longer (1.9 days [95% CI 1.2–2.6]). Compared with control, i.v. iron reduced RBC transfusion rate (11.5% vs. 26.4%) without incremental cost [88].

Thus, the use of newer i.v. iron formulations (e.g. iron isomaltoside 1000 or ferric carboxymaltose) allows the rapid administration of larger single doses ($\geq$ 1000 mg), and are more convenient both for the patient (e.g. fewer hospital visits, less time off work) and the health system (e.g. less visits to day hospital, less ambulance transfers, less total cost) [40, 86–89].

When comparing i.v. iron with other interventions implemented to reduce blood transfusion and/or placebo, it would be interesting to include the costs of postoperative complications and other clinical endpoints as well. Anaesthetists and surgeons should consider pre-operative iron deficiency not as a single 'point', although its treatment is essential. Instead, this should trigger a peri-operative bundle of care, known as Patient Blood Management, started at the time that surgery is booked and carried on until full recovery from the surgical intervention has occurred. This should be planned and documented pre-operatively, both in urgent and elective patients [90–92]. We believe there is ample evidence to support peri-operative blood management within the context of an evidence-based enhanced recovery programme to secure optimal interpretation of the intervention [93].

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